Intradermal naked DNA vaccination for mounting tumor-specific immunity in stage IV melanoma patients: a phase I clinical study

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Objective: Primary objective: 1.) To study the toxicity of naked DNA vaccines encoding CD8+ T cell epitope from melanosomal antigen MART-1 genetically linked to the gene encoding domain 1 of tetanus toxin subunit C by dose escalation in advanced-...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON35508

Source
ToetsingOnline

Brief title
DNA vaccination in metastatic melanoma

Condition

- Metastases

Synonym
melanoma; skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: NKI-AVL

Source(s) of monetary or material Support: KWF kankerbestrijding

Intervention

Keyword: DNA vaccine, intradermal, melanoma, Phase I study

Outcome measures

Primary outcome

Main study parameters/endpoints:

1.) Dose limiting toxicity of intradermal DNA vaccination using a plasmid

encoding tetanus toxin fragment c and an immunodominant HLA-A2 binding MART-1

peptide.

2.) Unacceptable toxicity of the use of a new device for intradermal delivery

of plasmid DNA.

Secondary outcome

1.) Immunological response against MART-1 in blood and biopsy material

2.) Objective clinical responses according RECIST

Study description

Background summary

Advanced-stage melanoma has a very poor prognosis. With standard chemotherapy consisting of single agent dacarbazine or DTIC an objective response rate of 10-15% can be achieved, very few of which are durable. Hence, the need for novel treatment strategies is high, and most strategies being developed aim to raise melanoma-specific T cell immunity. Naked DNA vaccination appears to be a powerful and safe strategy to mount antigen-specific cellular immunity.
Recently, we have developed a novel intradermal DNA delivery strategy. We make use of a permanent make-up or tattoo device to inject a DNA vaccine into the skin through thousands of skin punctures. This strategy has been developed in a mouse model and validated in a non-human primate model.
Patients with disease progression upon standard chemotherapy will be asked to participate in this phase I clinical trial. The DNA vaccine encodes a fusion

protein of the non-toxic domain 1 of tetanus toxin fragment c and the MART-1 epitope (ELAGIGILTV) under the CMV early promoter.

Study objective

Objective:
Primary objective:
1.) To study the toxicity of naked DNA vaccines encoding CD8+ T cell epitope from melanosomal antigen MART-1 genetically linked to the gene encoding domain 1 of tetanus toxin subunit C by dose escalation in advanced-stage melanoma patients with disease progression upon standard chemotherapy.
2.) To study the toxicity of a novel intradermal application strategy employing a permanent make-up or tattoo device.

Secondary objective:
1.) To study the efficacy of this naked DNA vaccine in inducing tumor-specific T cell immunity as measured by accumulation of MART-1-specific T cells at the vaccination site in skin biopsies and MHC tetramer staining of peripheral blood T cells.
2.) To study objective clinical responses
3.) To measure PFS and OS

Study design

Study design: Dose escalating phase I clinical trial
Dose levels: 0.5 mg; 1 mg; 2 mg; 4 mg

Intervention

Intervention: Intradermal DNA vaccine delivery by permanent make-up device on days 1, 3, and 6 and boost vaccination 4 weeks later.

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Eligible (HLA-A2+) patients will undergo a tumor biopsy to reveal expression of MART-1 and HLA class I by tumor cells. If present patients will receive intradermal DNA vaccination on days 0, 3, and 6, and boost vaccinations after 4 weeks (days 28, 31, and 34). At time points 1, 3, 4, 6, 8, 9, 12, 16 weeks patients will be seen at the outpatient clinic including physical examination and evaluation of toxicity. Blood and urine samples will be taken and frozen for analyses. Prior to vaccination, at t=14 days and t=42 days a skin biopsy will be taken from the vaccination site, and at day 42 also from a non-vaccination site.
For this group of patients no standard treatment exists. Their median life expectancy is less than 6 months. Vaccination using melanoma antigens is being

studied extensively worldwide and is in general non-toxic. DNA vaccination is considered a safe mode of vaccination. The vaccine that is being used in this clinical trial does not contain factors favoring integration, nor does it contain sequences that can lead to replication, or that can become part of viruses or bacteria. Preclinical data show that intradermal DNA vaccination using a permanent make-up device is much more potent than classic intramuscular DNA vaccination. Tattooing of skin is a commonly used method for treatment of scars or as part of reconstructive surgery (nipple tattooing after breast reconstructive surgery for breast cancer patients). It may induce a burning sensation during tattooing, which will stop the moment the tattooing is ended. Using this method DNA will be applied intra-epidermally (in the epidermis), therewith limiting spread to other tissues (in contrast to intramuscular of intravenous delivery). We therefore consider the physical discomfort associated with participation in this study as mild. As for participation in any phase I clinical study the intensity of site visits, physical exams, blood tests and other tests, is not different in this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Age above 18 years
• Performance score: WHO 0 or 1
• Life expectancy of >= 3 months
• Histologically or cytologically proven metastatic melanoma.
• Expression of MART-1.
• HLA-A*0201 positive.
• Evaluable disease.
• Disease progression after chemotherapy-based treatment.
• Adequate bone marrow (WBC > 3.0/nL, platelets > 100/nL), renal function (creatinine clearance > 40 mL/min, and liver function (bilirubin < 1.5 x ULN, normal blood coagulation)
• Willing and able to undergo the planned study procedures

Exclusion criteria

• Previous MART-1-specific immunotherapy.
• Patients with severe cardiac, respiratory, or metabolic disease.
• Symptomatic brain metastases.
• Use of systemic steroids or other immunosuppressive drugs.
• Use of oral anticoagulant drugs.
• Other cancers, except basal cell carcinomas or cervical CIS.
• Severe infections requiring antibiotics.
• Lactation or pregnancy
• Not willing to take adequate contraceptive measures.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-01-2009
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	none

Ethics review

Approved WMO Date:	04-06-2008
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-09-2008
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-03-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-03-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-03-2010
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-04-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2008-000100-91-NL
CCMO	NL20284.000.08